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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,380	08/02/2001	Charles Mark Ensor	PHOE-0061	7237

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EXAMINER
PATTERSON, CHARLES L JR

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/921,380	Applicant(s) ENSOR ET AL.	
	Examiner Charles L. Patterson, Jr.	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PEG-5,000 or PEG-20,000 bounded to uricase at unknown residues using a methoxy-SS-polyethylene glycol derivative, does not reasonably provide enablement for claims of the scope of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches that when the methoxy-SS-polyethylene glycol derivation of PEG-5,000 or PEG-20,000 is used to PEGylate uricase from *Candida utilis*, the conjugate has a longer "circulating half-life" than the unmodified uricase while retaining about 58 to 78% of its activity. It is not specified how or in what organism this "circulating half-life" is measured, but from page 23, lines 20-25 it is inferred that the measurement is in the mouse bloodstream. Although the Lys residues listed in e.g. claim 20 are recited in the specification as places where the PEG is to be not to be attached, there is absolutely nothing in the specification that teaches where the embodiment exemplified by applicant has the PEGs attached or what effect attaching or not attaching the PEG to these sites would have. There is nothing indicating what effect using all the different PEGs from 10,000 - 30,000 would have, not what effect using the linking groups in claim 1 would have. There is not even a teaching as to what linking group the use of a methoxy-SS-polyethylene glycol derivative will produce.

Claims 26-30 and 45-47 are drawn to "[a] method of enhancing the anti-uric acid activity of uricase comprising" bounding the uricase to PEG. There is absolutely nothing in the specification that would teach this embodiment. As discussed *supra*, the specification teaches that PEGylation will increase the "circulating half-life", but it does not teach that it will increase the anti-uric acid activity. As shown by Table 1, PEGylation actually decreases the uricase activity.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 13-21, 39 and 44 rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Caliceti, et al. (U). The instant reference teaches a uricase molecule from *Candida utilis* bound to polyethylene glycol 10,000. The linking group is not specified but if it is not one of those listed it is maintained that it would

have been obvious to use this linkage, absent unexpected results. The location of the bounds are not specified but it is maintained that it is one of the locations in claims 13-20, absent convincing proof to the contrary.

Claims 1-7, 13-21, 39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caliceti, et al. (U) in view of Gloger, et al. (BG). The primary reference is characterized *supra*. Gloger, et al. teach in column 1, lines 30-33 that uricase may be obtained from *Candida utilis* or *Aspergillus flavus*. It would have been obvious to one of ordinary art to obtain the uricase from either of these sources, absent unexpected results.

Claims 1-5, 8, 13-21, 39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caliceti, et al. (U) in view of Chua, et al. AB). The primary reference is characterized *supra*. Chua, et al. teach that uricase can be obtained from *Arthrobacter protoformiae*. It would have been obvious to one of ordinary art to obtain the uricase from this source, absent unexpected results.

Claims 1-7, 9-25 and 31-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gloger, et al. (BG) in view of either of Davis, et al. (A) or Zapilsky, et al. (AY). Gloger, et al. teach that uricase can be obtained from both *Candida utilis* and *Aspergillus flavus*.

Davis, et al. teach that adding polyethylene glycol (PEG) to enzymes will make them substantially non-immunogenic and cause them to retain a substantial proportion of their activity. In column 2, lines 56-58 it is taught that molecular weights of 500 - 20,000 daltons for the PEG is preferred. In the table in column 16, lines 41-54 it is shown that as the size of the PEG conjugated to insulin increases the activity also increases (PEG 750 has an

activity of 72 while PEG 2,000 has an activity of 90). It would have been obvious to one of ordinary skill in the art to obtain the uricase from the sources taught by Gloger, et al. and to use PEGs of molecular weights 10,000 - 20,000 in view of the teachings of Davis, et al. This ordinary artisan would have taken the teachings in column 2 that 500 - 20,000 molecular weight PEG was preferred along with the teachings in the table in column 16 that the activity of an enzyme increased with increasing molecular weight to vary the PEG added to the enzyme up to 20,000 with the expectation that the activity would increase.

Zapilsky, et al. teach in the first paragraph of section 21.2 that "the useful molecular weight range [of PEG] is 2,000 - 20,000 daltons. In Table I, page 361 it is taught that for alkaline phosphatase as the molecular weight of PEG increases from 4,000 to 20,000, the activity increases from 72% of the native enzyme to 80%. It would have been obvious to one of ordinary skill in the art to obtain the uricase from the source taught by Gloger, et al and to use PEGs of molecular weight 10,000 - 20,000 in view of the teaching of Zapilsky, et al. This ordinary artisan would have taken the teaching in section 21.2 and on page 361 to indicate that using increasing molecular weights of PEG up to 20,000 would lead to higher activity of the enzyme.

Claims 1-5, 8-25 and 31-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chua, et al. (AB) in view of either of Davis, et al. (A) or Zapilsky, et al. (AY). Chua teach that uricase can be obtained from *Arthrobacter protoformiae*.

Davis, et al. teach that adding polyethylene glycol (PEG) to enzymes will make them substantially non-immunogenic and cause them to retain a substantial proportion of their activity. In column 2, lines 56-58 it is taught

that molecular weights of 500 - 20,000 daltons for the PEG is preferred. In the table in column 16, lines 41-54 it is shown that as the size of the PEG conjugated to insulin increases the activity also increases (PEG 750 has an activity of 72 while PEG 2,000 has an activity of 90). It would have been obvious to one of ordinary skill in the art to obtain the uricase from the sources taught by Chua, et al. and to use PEGs of molecular weights 10,000 - 20,000 in view of the teachings of Davis, et al. This ordinary artisan would have taken the teachings in column 2 that 500 - 20,000 molecular weight PEG was preferred along with the teachings in the table in column 16 that the activity of an enzyme increased with increasing molecular weight to vary the PEG added to the enzyme up to 20,000 with the expectation that the activity would increase.

Zapilsky, et al. teach in the first paragraph of section 21.2 that "the useful molecular weight range [of PEG] is 2,000 - 20,000 daltons. In Table I, page 361 it is taught that for alkaline phosphatase as the molecular weight of PEG increases from 4,000 to 20,000, the activity increases from 72% of the native enzyme to 80%. It would have been obvious to one of ordinary skill in the art to obtain the uricase from the source taught by Chua, et al and to use PEGs of molecular weight 10,000 - 20,000 in view of the teaching of Zapilsky, et al. This ordinary artisan would have taken the teaching in section 21.2 and on page 361 to indicate that using increasing molecular weights of PEG up to 20,000 would lead to higher activity of the enzyme.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 703-308-1834. The examiner can normally be reached on Monday - Friday, 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
November 18, 2002